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Multimodality Therapy of an Acquired Factor V Inhibitor

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Acquired inhibitors of factor V are rare causes of clinical bleeding, whose severity ranges from mild to life-threatening. Optimal treatment of patients with factor V inhibitors is uncertain. We report on our successful treatment approach in a patient with spontaneous, life-threatening intracranial bleeding caused by a factor V inhibitor. The patient deteriorated after initial treatment with fresh-frozen plasma and platelet transfusions. He was subsequently treated with a combination of plasma exchange and chemotherapy, which led to complete recovery. Our experience suggests that plasma exchange may be lifesaving in cases of severe bleeding caused by factor V inhibitors. The use of plasmapheresis in conjunction with chemotherapy is an efficacious and well-tolerated treatment and should be considered in patients with factor V inhibitors. © 1996 Wiley-Liss, Inc.

Key words: factor V inhibitor, plasmapheresis, plasma exchange

INTRODUCTION

In the absence of hemophilia, inhibitory antibodies to specific coagulation factors that result in clinical bleeding are uncommon, and the majority are targeted against factor VIII [1]. By 1994, only about 40 cases of acquired factor V inhibitors had been reported in the literature [2–6]. However, there has been a recent increase in the number of reports of factor V inhibitors, possibly associated with the increasing use of topical bovine thrombin preparations [7–11]. In contrast to the consistently reported severe bleeding tendencies in patients with factor VIII inhibitors, clinical experience with factor V inhibitors is more variable, ranging from severe bleeding to thrombosis [2–6,12].

The rarity of factor V inhibitors, their marked clinical variability, and the high rate of spontaneous remission have combined to make it difficult to evaluate treatments. Miletich et al. [13] first reported that platelet transfusions have a role in managing factor V inhibitors, and this observation has been supported by other investigators [14–17]. While treatment of bleeding episodes with factor VIII inhibitors has included human plasma-derived and recombinant factor VIII as well as porcine factor VIII, similar replacement products for factor V are not available. Furthermore, products aimed at bypassing the point of inhibition, such as factor IX-containing concentrates and recombinant factor VIIa, have been useful for factor VIII inhibitors but would not be predicted to work as well in patients with factor V inhibitors [1]. Other strategies in the treatment of factor VIII inhibitors have included intravenous immunoglobulin, glucocorticoids, chemotherapy, plasmapheresis, and the staphylococcal protein A column, and some of these approaches may be effective in the treatment of factor V inhibitors as well [5,16]. Here we report on our therapeutic approach to the successful treatment of a patient with life-threatening bleeding caused by factor V inhibitor.

CASE REPORT

A 75-year-old paraplegic white man was in his usual state of health until 3 weeks prior to admission, when he developed a urinary tract infection that was treated with ciprofloxacin. Eight days prior to admission he was seen as an outpatient because of a bloody discharge from a decubitus ulcer present on his right foot. He was noted to have a prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), and was started on a 1-week course of oral vitamin K. Three days prior to admission the patient developed a headache accompanied

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by nausea, vomiting, and short-term memory loss. On the day of admission a CT scan of the head showed a left subdural hematoma, with a 1-cm left-to-right shift of the lateral ventricles.

The patient has been paraplegic since a traumatic spinal injury in 1974. He has a neurogenic bladder with an indwelling suprapubic catheter, and he has been treated for multiple urinary tract infections in the past. He also has hypertension, noninsulin dependent diabetes mellitus, and peripheral vascular disease. The patient had a deep venous thrombosis of the left leg 9 years ago. There was no personal or family history of a bleeding disorder. Two years prior to the current admission, PT and aPTT were normal. Medications on admission were 5 mg vitamin K po qd, 5 mg glipizide po qd, and 50 mg metoprolol po bid.

On physical examination the patient appeared acutely ill but was alert. His pulse was 90 bpm, BP 158/98, and respirations 24/min, and he was afebrile. On neurological examination, he had a paraplegia extending to the L1 spinal level that was unchanged from his baseline. Fine finger movements of his right hand were slightly impaired, but no other new focal sensory or motor deficits were noted. He had a small ulceration of his right first toe as well as a sacral decubitus ulcer with mild bleeding.

Laboratory data on admission included a PT of 32.9 sec and aPTT of >106 sec (normal ranges: PT, 11.4–13.2 sec; aPTT, 24.1–32.3 sec). The PT partially corrected from 32.8 sec to 18.2 sec on a mixing study with an equal volume of normal pooled plasma; a similar mixing study showed partial correction of the aPTT (94 to 42 sec), and after 1 hr of incubation at 37°C, the aPTT mix was 50.6 sec. The thrombin time was 20.9 sec (normal range: 11.1–18.5 sec). The fibrinogen level was 375 mg/dl, and no fibrinogen degradation products were detected. A dilute Russell's viper venom time was abnormal, suggesting the possibility of a lupus anticoagulant, but a phospholipid neutralization assay was not confirmatory. The data were consistent with a phospholipid-independent inhibitor of the common coagulation pathway. Prothrombin and factor X levels were normal, and factor V activity was <6%. These studies led to the presumptive diagnosis of a factor V inhibitor. This inhibitor was subsequently isolated by fractionating the plasma on a staphylococcal protein A column. The IgG-containing eluate inhibited the clotting time, supporting the diagnosis of an antibody-mediated inhibitor (Fig. 1).

On the first hospital day the patient received an infusion of 1,600 ml of fresh-frozen plasma (FFP) and two units of single-donor platelets (SDP), with a partial correction of his coagulation parameters (Fig. 2). On the second hospital day he became extremely lethargic, prompting a repeat head CT scan demonstrated that the hematoma had approximately doubled in size. The patient soon became comatose, and underwent an emergency craniotomy for evacuation of the subdural hematoma and placement of a subdural drain. The patient received another 900 ml of FFP and one unit of SDP over the next several hours. That evening, therapeutic plasma exchange (1.5 × plasma volume) was initiated using FFP as the replacement fluid, with the intent to remove the inhibitor as well as to supply maximal exogenous factor V to the patient in a short period of time. About 250 ml of blood were collected from a subdural drain overnight, but the bleeding rapidly declined and a subsequent CT scan showed no recurrence of the hematoma. The patient's neurological status markedly improved during that time. His aPTT was normal (29.9 sec), and his PT was 14.6 sec following the first pheresis procedure. A 1.5 × volume plasma exchange using FFP as the replacement fluid was performed daily for the next 3 days. As shown in Figure 2, the PT shortened immediately following each plasma exchange, but would subsequently prolong the following day, suggesting reequilibration of the inhibitor from the extravascular fluid and continued inhibitor production. As an adjunct to plasma exchange, an immunosuppressive regimen was begun on the third hospital day, consisting of 500 mg cyclophosphamide IV, 2 mg vincristine IVP, and 100 mg prednisone po. He received 200 mg cyclophosphamide po and 100 mg prednisone po for the subsequent 3 days.

After four pheresis procedures, the PT was 13.3 sec and the factor V level was 73%. On the sixth hospital day, the patient was given an infusion of 1,350 ml FFP rather than plasma exchange, and his PT remained stable. One week after cessation of plasma exchange, his PT was 12.6 sec and his factor V level was 112%.

The patient continued to do well clinically, and was transferred to a rehabilitation service. Two weeks after the plasma exchange was completed, his PT and aPTT again began to prolong, and his factor V level was 20%. No bleeding was detected. He was treated with approximately 900 ml of FFP per day for 3 days, and he received a second cycle of identical immunosuppressive therapy. His factor V level normalized to 88% within 2 weeks, and was 97% 2 weeks later. No subsequent therapy was given, and he remains clinically stable 5 months after treatment, with a normal PT and aPTT.

DISCUSSION

Patients with hereditary or acquired deficiencies of factor V may have severe bleeding disorders, supporting the fact that factor V is essential for normal hemostasis. Factor V circulates in plasma as a single chain 330-kD glycoprotein and is also found in the alpha granules of platelets. The relative roles of plasma and platelet-associated factor V in normal hemostasis are not totally clear. The importance of plasma factor V has been demonstrated in factor V-deficient patients who receive infusions of plasma to prevent surgical bleeding [16,17].

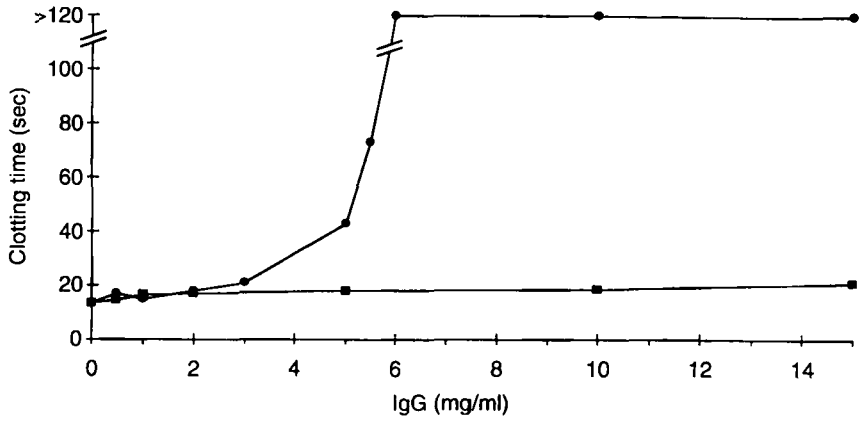

Fig. 1. Effect of IgG on clotting time. Patient IgG was isolated on a staphylococcal protein A column. After elution, the sample was dialyzed and concentrated to a final concentration of 25 mg/ml. Fifty μl of pooled human plasma was added to patient IgG or control human IgG and preincubated for 10 min at 37°C prior to adding 50 μl rabbit brain thromboplastin. Clotting time was determined using a fibrometer and was performed in duplicate. Final concentration of IgG is shown for control human IgG (■) and isolated patient IgG (•).

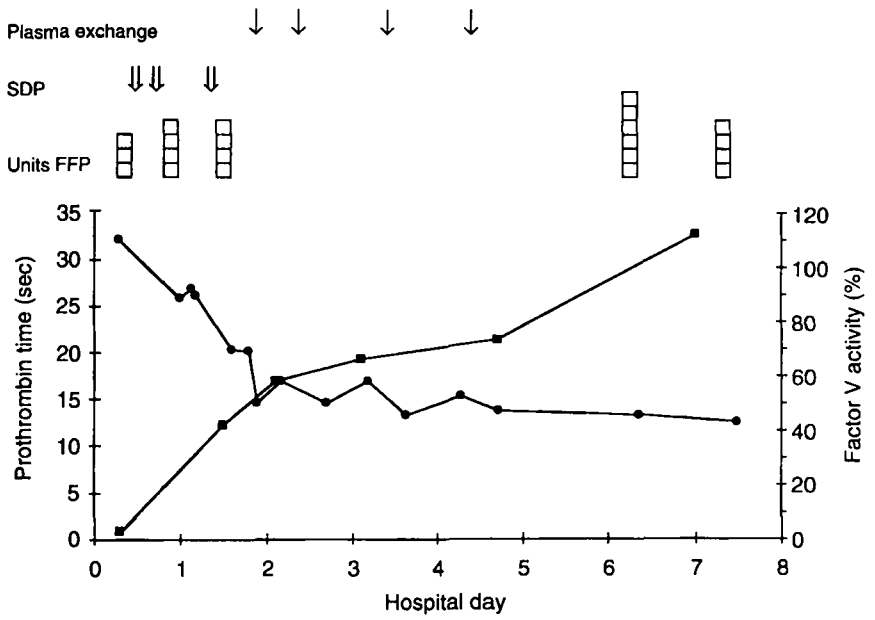

Fig. 2. Initial hospital course in treatment of factor V inhibitor. Treatment with FFP is identified by open squares; each unit is approximately 225 ml. Units of single-donor platelets (SDP) are identified (⇓). Each plasmapheresis exchanged 5,000–6,500 ml of FFP. PT (•) and factor V activity (■) are shown.

Several reports in the literature suggest that platelet-associated factor V is likely to be an important pool for hemostasis in vivo [2–6, 13–16]. Tracy et al. [15] reported a family study in which affected members displayed a bleeding disorder in the context of extremely low factor V activity in platelets but relatively normal plasma factor V activity, suggesting a crucial role for platelet factor V. This defect has recently been proposed to be in multimerin, a platelet alpha-granule protein that binds factor V [18].

In contrast to factor VIII, platelet-associated factor V seems to have a unique role in the treatment of some patients with factor V inhibitors. Nesheim et al. [2] demonstrated that platelet factor V is relatively protected in the presence of a potent plasma factor V inhibitor, suggesting a therapeutic role for platelet transfusions against factor V inhibitor. Chediak et al. [14] also reported successfully treating a patient with a factor V inhibitor by administering platelet concentrates alone. By comparison, our patient demonstrated no clinical response to platelet

transfusions. One explanation for this observation is that this patient demonstrated a fast-acting antibody. Our mixing studies of the aPTT and PT showed significant immediate inhibition of normal plasma factor V activity in vitro. In contrast to some factor VIII inhibitors, this effect was only modestly enhanced with a 1 hr incubation at 37°C. Furthermore, a fast-acting antibody may potentially block factor Va activity shortly after it is released from platelets, limiting the amount of blood clot that could otherwise be successfully formed.

Plasma exchange offers some advantages over simple plasma infusion or platelet transfusions. It allows for the administration of large volumes of plasma (5,000–6,500 ml in this case) containing factor V over a short period of time without risk of volume overload. In addition to physical removal of inhibitor from the plasma, the infusion of large amounts of factor V is presumed to neutralize some of the inhibitory activity. One molecule of factor V may have several antibody-binding epitopes. Such large antibody-antigen complexes may more likely be removed by therapeutic pheresis.

The regimen of cyclophosphamide, vincristine, and prednisone has been successfully used in the treatment of acquired factor VIII inhibitors [19]. Our patient had low factor V activity 2 weeks after his initial response, suggesting incomplete immunosuppression by the first cycle of combined therapy. In our unpublished experience as well as that of others with factor VIII inhibitors, repeated cycles of immunosuppressive therapy are frequently required for complete long-term recovery [19]. This regimen appears to be well-tolerated and effective in augmenting immediate treatment with plasma exchange and factor replacement in patients with factor V inhibitors, and should be considered as a potentially effective approach for treatment of patients who do not respond to plasma or platelet transfusions.

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